Orlistat over the counter

Has a minimal effect on obesity and is no substitute for a healthy lifestyle

RESEARCH, p 1194

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Orlistat (Xenical, Roche) is one of a handful of antiobesity drugs that, when used appropriately, can cause significant weight loss with acceptable safety.[1] It inhibits the gut lipases that hydrolyse ingested triglyceride (which constitutes almost all dietary fat) and decreases the absorption of lipid, which is the most energy dense nutrient. In clinical trials, such as those included in a systematic review by Rucker and colleagues published in this week's *BMJ*, up to a third of obese people taking the standard therapeutic dosage (120 mg three times daily) lost at least 10% of their initial weight.[1] This is the threshold value that is generally assumed to confer clinically important reductions in the metabolic and cardiovascular risks associated with obesity.[2]

The drug acts only in the gut lumen and—apart from potential deficiencies of fat soluble vitamins with chronic use—it seems to be safe. The main side effect is steatorrhoea (excess fat in the faeces), usually as a result of eating food high in fat, which obese people should avoid. Other side effects include faecal incontinence. Orlistat is widely prescribed under medical supervision to supplement—not replace—lifestyle modifications, primarily eating less and exercising more, which remain the key to success in managing obesity.

In 2006, the American Food and Drug Administration granted GlaxoSmithKline (GSK) approval to sell a 60 mg preparation of orlistat (Alli) "over the counter"—that is, directly from pharmacies and without medical supervision. Clinical trials indicated that three 60 mg doses a day were almost as effective as the 120 mg regimen and that up to a quarter of people might achieve a weight loss of 10% or more.[3] GSK provides an information pack and website (www.QuestionEverything.com), with guidance about healthy eating (and helpful suggestions about choosing clothes to deal with the drug's side effects). To date, sales have been brisk (>$155m; >£75m; >€108m) and no serious adverse events have been reported on the company's website.

GSK has now applied to the European Agency for the Evaluation of Medicinal Products to sell Alli over the counter throughout Europe. At first glance this seems reasonable. Orlistat works and is safe, and people should be free to spend their money as they wish. Besides, we need all the weapons at our disposal to fight obesity, and this might help in some cases without putting further strain on hard pressed medical services. However, I have reservations.

Firstly, it is unlikely that many users will see significant health benefits. Clinical trials inevitably show antiobesity drugs at their best, because the participants are relatively motivated and are supported by dedicated staff who reinforce lifestyle advice. We do not know how well Alli would perform without such support. Moreover, the benefit of orlistat over placebo in clinical trials is small—typically 2-5 kg after one year,[1 3] and declining to 2.7 kg after four years.[4] One uncontrolled, open label trial that deliberately omitted attempts to improve lifestyle found that orlistat 120 mg three times daily for six months achieved a mean weight loss of 5 kg, which was accompanied by small but significant improvements in blood glucose, lipids, and blood pressure.[5]

Under real world conditions Alli might not fare so well because many people will not persevere with treatment for long enough to see benefits. Obese people have great but sadly unrealistic expectations of antiobesity drugs—for example, that they will lose 25% of their weight within 12 months[6]—and even in clinical trials up to 40% of subjects drop out.[3 7] People who take these drugs without comprehensively changing their lifestyle will probably lose less weight than those who make lifestyle changes, and they are likely to be more disappointed with the scale and rate of weight loss.[6] Disillusionment is an important reason for patients discontinuing treatment, and it may set in early with casual users of antiobesity drugs, whose motivation is often short term and cosmetic rather than long term or medical. As one online provider of diet pills (www.ConsumerPriceWatch.net) puts it, "our top ten best diet pills will help You get the body of your dreams Safely, Quickly and Affordabley [sic] without getting ripped off!" Orlistat's tendency to cause faecal incontinence—airily dismissed by a senior GSK executive as the "oops factor"[8]—will not encourage adherence to the drug, especially as the problem can be neatly avoided by omitting a dose whenever a high fat meal is going to be eaten.

Possibly, few users will even finish their first pack of Alli, let alone buy a second, and the drug may cause only a small and transient downward blip in the otherwise inexorable climb in weight and cardiometabolic risk. We have no strong evidence that the benefits of short term weight loss are carried forward if weight is regained—which always happens when drug treatment stops, unless the person's obesogenic lifestyle has also been corrected. The net health gain of taking Alli without medical supervision is therefore probably minimal.

Even though orlistat seems to be innocuous, selling it over the counter could cause insidious collateral damage. Obesity is a life sentence. Some remission can be earned by good behaviour, but this requires affected people to

fight against strong societal and commercial forces and change their lifestyle radically. Globally, obesity is spiralling out of control and will only be reined in by public health campaigns that somehow persuade people to eat less and exercise more. Selling antiobesity drugs over the counter will perpetuate the myth that obesity can be fixed simply by popping a pill and could further undermine the efforts to promote healthy living, which is the only long term escape from obesity.

The only real beneficiary will be GSK. We will never know whether Alli is useful, as there will be no proper follow-up. Viewed commercially, proof of efficacy is irrelevant—money will roll in for as long as the obesity pandemic continues to yield enough people prepared to pay for a quick fix solution to their unhappiness. On the basis of criteria that include value, customer feedback, reorder rates, safety, and packaging, Alli is currently ranked only 57th out of 200 by Consumer-Price-Watch.net, whose top ten diet pills include several products that are known to be dangerous or are devoid of evidence that they actually work (or both). Nevertheless, Alli will probably generate income for GSK.

So what should we recommend? People tempted to try Alli might be advised that taking it without medical supervision may achieve an average daily energy deficit of only 0.4 MJ (100 kcal)—equivalent to leaving a few French fries on the plate, eating an apple instead of an ice cream, or (depending on enthusiasm and fitness) having 10-20 minutes of sex. The European Agency for the Evaluation of Medicinal Products should remember the World Health Organization's key recommendations[9 10]—that eating less and exercising more must remain the cornerstones of managing obesity—and reflect on the damage that will be caused if this crucial strategy is undermined.

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Mortality in men admitted to hospital with acute urinary retention

Is highest in men with comorbid conditions, so multidisciplinary care is needed

RESEARCH, p 1199

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Acute urinary retention is the sudden inability to micturate; it is usually painful and requires treatment with a urinary catheter.[1] Risk factors are increasing age, especially in men; urological conditions such as benign prostatic hyperplasia, prostate cancer, and urethral stricture; medical conditions such as constipation and diabetes mellitus; bed rest; surgery; and the use of certain drugs.[2] Its incidence in the general population has mostly been studied in men, and it varies between 2.2 and 6.8 per 1000 person years. Acute urinary retention is generally treated **immediately with a urinary** catheter. After the acute period, most men will be offered a trial **without catheter, often in combination** with α adrenergic **blockers. Prostate surgery will be** considered if this trial fails.[3-7]

Few data are available on mortality in patients with acute urinary retention. A retrospective cohort study in this week's *BMJ* by Armitage and colleagues is the first to study long term mortality in men admitted to hospital for a first episode of acute urinary retention.[8] The study uses data from the hospital episode statistics database and the mortality database of the Office for National Statistics in the United Kingdom. The authors found that mortality was high—one in seven men with spontaneous acute urinary retention (no evidence of precipitating factors other than benign prostatic hyperplasia) and one in four men with precipitated acute urinary retention (all cases that were not spontaneous) died in the first year. The risk of dying increased with age and comorbidity (measured by the Charlson score). In the first year after hospital admission, 16% of men with precipitated acute urinary retention and no comorbidity died compared with 38% of similar men who also had comorbidity.

The study also compared mortality at one year with mortality in the general male population of the UK. Overall, mortality at one year in men admitted to hospital for acute urinary retention was two to three times higher than for the general male population. The highest relative increase in mortality was seen in men aged 45-54 and in those with precipitated acute urinary retention **(standardised mortality ratio 10.0 for** spontaneous **acute urinary retention and 23.6 for the** precipitated form).

Benign prostatic hyperplasia has been associated with comorbidities such as diabetes mellitus, hypertension, and the metabolic syndrome.[9] Armitage and colleagues' study is important, not only because it is the

first to study mortality after hospital admission for acute urinary retention, but also because it confirms the high prevalence of comorbidities such as cardiovascular disease, diabetes mellitus, and chronic pulmonary disease in people with urinary retention. Because mortality was highest in the presence of comorbid conditions, people presenting with acute urinary retention should be given a urological examination and a multidisciplinary review to identify and treat comorbidity early.

Several questions remain unanswered. Firstly, Armitage and colleagues focused on the effects of comorbidity and did not consider the effects of concomitant drugs. Opioids and drugs with anticholinergic or adrenergic activity increase the risk of acute urinary retention. Thus, the association between comorbidity and acute urinary retention could be partly explained by the use of drugs for the treatment of chronic conditions, such as inhaled anticholinergics for chronic obstructive pulmonary disease and opioids for the relief of chronic severe pain. Secondly, it would be interesting to know whether mortality at one year varies with the type of treatment (trial without catheter versus prostate surgery) and whether the increase in mortality is seen not only in people admitted to hospital but also in those receiving care in the community. Finally, the conclusion that people with acute urinary retention should be screened for comorbidity at the time of admission seems sensible, but prospective studies are needed to measure the effect of this approach on mortality rates.

If mortality really is higher in men admitted to hospital for acute urinary retention, we should try to prevent acute urinary retention in people with benign prostatic hyperplasia. Randomised controlled trials have shown that 5α reductase inhibitors reduce the risk of acute urinary retention, especially in men with severe symptoms, large prostates, and high concentrations of prostate specific antigen. Risk was reduced most in men treated with a 5α reductase inhibitor combined with an α_1 adrenergic blocker.[10 11] A retrospective cohort study of men with benign prostatic hyperplasia, however, showed that about 50% of those with acute urinary retention presented with urinary retention as the first symptom of their underlying prostatic hyperplasia.[12] For these men, pharmacological prevention will be too late.

In conclusion, because the increased mortality seen in men admitted to the hospital for acute urinary retention is probably the result of comorbid conditions and frailty, multidisciplinary care is warranted in these men.

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Recognising and responding to acute illness in patients in hospital

Leadership, culture change, education, support, and regular auditing are key

PRACTICE, p 1210

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The recognition of and response to potentially life threatening acute illness on hospital wards is of increasing concern. Changes in the type and availability of staff combined with the need to manage patients with increasingly complex problems have highlighted this concern.

Patients who develop severe organ failure often have abnormal physiological signs, sometimes for hours before their final "collapse." Attempts to improve how we identify and manage these patients disregarded the lack of robust evidence,[1] and national policies and initiatives promoting new models of care were issued in England (critical care outreach services),[2 3] the United States (rapid response teams),[4] and Australia (medical emergency teams).[5]

In their paper in this week's *BMJ*, Buist and colleagues report their experience of a model that incorporates a method to improve the recognition of acute illness (medical emergency team calling criteria) with skilled personnel (the medical emergency team) to ensure a timely and appropriate response. The model is underpinned by an ongoing programme of education and support, both formal (an orientation programme for interns and a professional development course for medical registrars) and informal (introduction of an intensive care liaison nurse).[6]

During the last six years of a 10 year implementation period, they found a sustained reduction in the incidence of in-hospital calls for cardiac arrest

(used as a proxy for delayed or suboptimal clinical management) of 24% each year. If we assume that these results do not reflect a dilution effect from the increasing denominator of hospital admissions (of 25% over the six year period), or a more general decline in the incidence of in-hospital cardiac arrest in the hospital population, then they may indicate that the clinical management of these patients improved. This may have occurred either through a genuine reduction in cardiac arrests or more appropriate use of "do not attempt resuscitation" orders.

What can we learn from these results for our own healthcare systems, hospitals, and practices? And what gaps in our knowledge should be a priority for research in this area?

Buist and colleagues' experience indicates that leadership, culture change, education, support, and regular auditing of activity are important. Leadership was clearly important for ensuring successful implementation—the authors themselves showed such leadership. A culture change was needed and changing culture takes time—in Buist and colleagues' experience, 10 years. A formal and informal education and support programme was needed to reinforce the need for periodic, appropriate documentation of physiological observations; to educate staff about the importance and interpretation of abnormal physiological observations; to empower the more junior staff to make the call to the medical emergency team; and to reinforce the need for a non-negotiable obligation from more senior, experienced staff to attend the patient's bedside.

The importance of these lessons is supported by other research. The only multicentre randomised controlled trial of this model of care (MERIT) cites its short time frame for implementation of medical emergency teams as one reason for its failure to find an effect.[7] Other reasons, which were also noted in Buist and colleagues' study, included failure to make the call to the medical emergency team and delay in, or absence of, response.

Our recently completed qualitative study (122 in-depth interviews with relevant stakeholders in eight acute National Health Service hospitals)—part of a mixed methods evaluation of critical care outreach services in the NHS—highlighted the importance of leadership and the need for an "organisational entrepreneur" to ensure successful and sustained implementation.[8] Critical care outreach services created an important change in culture by facilitating connectivity, reducing communication difficulties, and enhancing the delivery of care across organisational, professional, and specialty boundaries. The importance of training, particularly informal training (reassuring ward staff was most often highlighted), and factors related to implementation including documentation, authority, communication, resistance, and delay were also highlighted (D Baker-McClearn, S Carmel, personal communication, 2007).

The biggest gaps in our knowledge relate to the best way to identify deterioration, the most appropriate staff to respond to deterioration, the level of education and support needed, and the overall cost effectiveness of this model of care.

Buist and colleagues use one of several physiological "track and trigger" warning systems for detecting patients who are deteriorating. A recent systematic review identified at least 25 of these warning systems; none met the requirements for a level 1 clinical decision rule and little rigorous evidence existed for their validity, reliability, usefulness, or diagnostic accuracy.[9] An assessment of 15 of these warning systems showed less than optimal diagnostic accuracy and provided no clear evidence of which method was best. Buist and colleagues provide no details of the diagnostic accuracy of their system but recognise that it could be improved.

Medical emergency teams and rapid response teams are staffed mainly by doctors, whereas critical care outreach services are staffed mainly by senior nurses. The optimum composition of a team or service, the best personnel to respond, and whether responses should be graded by the severity of the trigger are all unknown. Optimal diagnostic accuracy, grading of response, and an appropriate level of education and support will be essential for managing the workload and costs of delivering this model of care in the future.

The original objectives for the national policies and initiatives were the timely recognition of patients with potential or established critical illness followed by rapid attendance and initial management from skilled staff in an equitable manner across all acute hospital settings. To achieve this, we need to develop outcome measures for early identification of acute deterioration that can be used to evaluate and identify the most appropriate track and trigger warning system.

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Influence of pharmaceutical funding on the conclusions of meta-analyses

Original data are sound, but conclusions should be interpreted with caution

RESEARCH, p 1202

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Competing interests: RAE has worked as a consultant to drug companies for many years over a wide range of issues involving liability, parallel importation, and Food and Drug Administration matters. He has not worked for a drug company on conflicts of interest questions of the sort discussed here. The Institute for Policy Information, which has ties to the drug industry, provided financial support for a book he recently wrote.

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Differences in interpretation of results between meta-analyses funded by drug companies and those that are not rightly raise concerns about the reliability of studies funded by the industry.[1-5]

In this week's *BMJ*, Yank and colleagues offer further proof of the potential influence that the drug industry has on the outcomes of the studies they fund.[6] The study assesses the correlation between the "results" of meta-analyses about hypertensive drugs and the "conclusions" their authors draw from them. Even if we allow for the inevitable subjectivity of Yank and colleagues' review of the included meta-analyses and for the other potential sources of bias they recognise—unblinded review and somewhat arbitrary measures of financial ties—the key findings are likely to be robust and will draw the ire of the many critics of the drug industry.

Yank and colleagues show that studies funded by a single drug company have a 55% rate of favourable results that is transformed into a 92% rate for favourable conclusions, representing a 37% gap. The gap shrinks to 21% (57% to 79%) when two or more drug companies provide support. Yet the gap vanishes entirely for studies done by non-profit institutions alone or even in conjunction with drug companies. The clear inference is that impartial studies are more reliable. What accounts for these results? And what should be done about them?

In terms of explaining the results, the sample size of 124 studies is too small to allow the analysis to be broken down into smaller categories. Such refinement might be helpful to identify what characteristics beyond "financial tie" might account for the better or worse performance within studies funded by a single drug company. How much direct control does the drug company exercise over the study? Do its own doctors participate? These questions matter because any bias that asserts itself in meta-analyses is unlikely to disappear in ordinary clinical trials, where company experts commonly team up with outside experts. The proper mix of personnel and the introduction of sensible safeguards for independence could prove valuable in reducing any actual or perceived bias. Increased confidence in clinical trials remains vital, even if the actual skew in these areas turns out to be less robust than the one found in this study.

It has been suggested that drug companies should have a more restricted role in financing and organising clinical trials generally.[1-5] One proposal suggests that drug companies should contribute money to research institutions, which then spend the funds on whatever research they regard as appropriate.[7] But if we push too hard with these recommendations, industry support may dry up.[8 9] Around 40% of the studies Yank and colleagues analysed were done by single drug companies. Only slightly more than 20% were done by non-profit making organisations. At a guess, the 20% of the studies that had "no statement" would be distributed in a similar ratio—8% would be funded by a single drug company and only 4% by a non-profit making organisation. Accordingly, any strong prohibition on the involvement of drug companies would reduce the number of studies conducted by more than 60% if studies funded by multiple drug companies were also prohibited. We are unlikely to be able to find large new sources of funding under current circumstances.

We therefore face a dilemma. Do we want fewer studies of presumably better quality, or do we want more studies whose quality may be more biased? I would opt for the last option. Nothing in the work of Yank and colleagues suggests that the raw data from the drug sponsored studies were defective. The criticisms are directed to the optimistic inferences drawn from data. But these inferences are drawn from publicly available sources, which other investigators could presumably check without having to re-collect the original data from scratch. A sensible approach might be to encourage further dialogue by asking for editorial comment. These commentaries need not appear in the same journals as the original studies, assuming they are published. The commentaries could be published elsewhere to offer a balanced perspective, and the original authors could be invited to respond to any criticisms. In all likelihood, these critiques will subtly induce original authors to soften their basic claims.

Legal restrictions or requirements do not need to be imposed on drug company funding or participation in these studies. The medical profession already has voluntary means to improve its performance. As long as the disagreements lie in the interpretation of data and not the collection of data, the solution is not state regulation; rather, doctors should be warned to be cautious in interpreting the conclusions of studies. Indeed, the largest problem for drug innovation does not lie with these studies, but in the ever greater time and money needed to bring new drugs to market, where the price of delay is too often measured in lives lost.

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Implementing practice based commissioning

Is happening slowly but not necessarily surely

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In its recent report, the Audit Commission described the current state of implementation of practice based commissioning. The commission defined such commissioning as a way of managing financial risk as well as a means of improving services and use of resources. Under practice based commissioning, primary care trusts devolve indicative budgets to practices (practices do not receive the actual money, but operate within an agreed budget held and administered by the primary care trust) to give them financial incentives to manage referrals, and to commission and redesign services to make them more convenient, appropriate, and cost effective.

Practice based commissioning has been a central part of the government's current reforms of the National Health Service (NHS) since April 2005, when interested practices were first entitled to an indicative budget. Any assessment of progress must therefore be of interest in assessing the fate of government health policy overall.

The Audit Commission studied the second year of practice based commissioning (2006-7) in 16 primary care trusts. The study was based on semi-structured interviews with trust staff, selected general practitioners, and selected practice managers, combined with a survey of local general practitioners (20% response rate, unfortunately) and information from local audits of primary care trusts and NHS trusts. The study aimed to determine whether the financial incentive of devolving budgets to general practitioners had enabled primary care trusts to manage their financial resources better.

The report suggests that only modest progress has been made in implementing practice based commissioning. On the positive side, general practices had a better understanding of the financial consequences of their decisions and engaged more in managing their patients' use of secondary care (demand management). However, these achievements cost £98m (€137m; $203m) in payments to general practitioners to participate in practice based commissioning in 2006-7 (and this ignores the opportunity costs of staff time within primary care trusts).

Moreover, the Audit Commission identified a longer list of areas where progress had been slow or problematic and where more development was needed. Genuine engagement of general practitioners in practice based commissioning was not yet widespread, and the incentives to engage were not strong enough. Many primary care trusts had been unwilling to relinquish their control over commissioning priorities and needed to improve their support for practice based commissioning, particularly in relation to providing information and setting budgets. Service redesign and the transfer of care from secondary to primary care, though widely discussed, had progressed only modestly.

Perhaps most tellingly, many practices saw practice based commissioning more as a way to fund an increase in their provision of new services than as a means to commission health care from others or manage financial risk.

The commission's findings are consistent with our ongoing research. The inadequacy of support for practice based commissioners by primary care trusts—at least in the minds of general practitioners—was also identified in a recent national survey of practice based commissioning carried out in a sample of general practitioners by the Department of Health.

The similarities with research done in the 1990s into general practitioner fundholding and its extension—the "total purchasing pilots"—are striking. And, although practice based commissioning is not the same as general practitioner fundholding, as the Audit Commission makes plain, it shares several characteristics. It is most similar to total purchasing pilots which, like practice based commissioning, involved collaboration between a statutory commissioning organisation (then the health authorities) and a group of general practitioner fundholders, with the statutory body having the ultimate financial responsibility.

The advance of general practitioner fundholding and total purchasing pilots in the internal NHS market of the 1990s was checked by several factors that are familiar today—weak engagement of ordinary general practitioners not in leadership positions, insufficient management support from health authorities, and a lack of timely and accurate information on which to base budgets and commissioning decisions.

However, these two initiatives did lower the use of hospital services where this was their priority, despite these hurdles. Does this mean that, in time, practice based commissioning will be similarly successful? Not necessarily. General practitioner fundholding and total purchasing pilots had greater autonomy from the health authorities; these initiatives also had complete freedom to choose the practices they wished to work with and enjoyed stronger financial incentives than practice based commissioning.

So, is practice based commissioning the sick man of the NHS reforms? This would be too harsh a judgment. As the Audit Commission points out, their study took place during only the second full year of implementation. This may partly account for the modest progress made. Moreover, primary care trusts are putting the rigours of reconfiguration behind them and are about to enter a development phase intended to deliver "world class commissioning." If successful, the capacity of trusts to support practice based commissioning should improve. Surveys suggest that general practitioners support the idea of practice based commissioning, even if their practical engagement to date remains limited.

Nevertheless, practice based commissioning was first mentioned as an aspiration by the incoming Labour government in its first major policy document in 1997, and the first dedicated guidance emerged as far back as 2004. Against this timescale, progress can only be regarded as slow.